Journal of Intensive Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Intensive Medicine

journal homepage: www.elsevier.com/locate/jointm

Review

Diagnostic approach in acute hypoxemic respiratory failure

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ARTICLE INFO

Managing Editor: Jingling Bao/Zhiyu Wang

Keywords:
Acute hypoxemic respiratory failure
Acute respiratory distress syndrome
Diagnostic procedure
Diagnostic technique
Outcome

ABSTRACT

Acute hypoxemic respiratory failure (AHRF) is the leading cause of intensive care unit (ICU) admissions. Of patients with AHRF, 40 %–50 % will require invasive mechanical ventilation during their stay in the ICU, and 30 %–80 % will meet the Berlin Criteria for Acute Respiratory Distress Syndrome (ARDS). Rapid identification of the underlying cause of AHRF is necessary before initiating targeted treatment. Almost 10 % of patients with ARDS have no identified classic risk factors however, and the precise cause of AHRF may not be identified in up to 15 % of patients, particularly in cases of immunosuppression. In these patients, a multidisciplinary, comprehensive, and hierarchical diagnostic work-up is mandatory, including a detailed history and physical examination, chest computed tomography, extensive microbiological investigations, bronchoalveolar lavage fluid cytological analysis, immunological tests, and investigation of the possible involvement of pneumotoxic drugs.

Introduction

Acute hypoxemic respiratory failure (AHRF) is the leading cause of intensive care unit (ICU) admissions. In the multinational LUNG SAFE study,[1] 10 % of patients admitted to the ICU met the criteria for acute respiratory distress syndrome (ARDS). Of patients with AHRF, 40 %–50 % will require invasive mechanical ventilation during their stay in the ICU[2,3] and 30 %–80 % will meet the Berlin Criteria for ARDS.[1,3,4] While symptomatic supportive care of patients with AHRF is required immediately (i.e., admission to the ICU, administration of appropriate ventilatory support, management of associated organ failures), rapid identification of the underlying cause of AHRF is necessary before initiating targeted treatment, and in order to improve outcomes.[5] A diagnosis of ARDS requires that the AHRF is not exclusively or primarily related to cardiogenic pulmonary edema or fluid overload, atelectasis or lung collapse, pleural effusion, or pulmonary embolism.[6] The first step in the diagnostic approach to AHRF is therefore to investigate these conditions during initial assessments. The most common causes of AHRF reported in the FLORALI trial[3] were community-acquired pneumonia (63.5 %), hospital-acquired pneumonia (11.9 %), extrapulmonary sepsis (5.2 %), and aspiration and near drowning (1.9 %). Less common risk factors for ARDS reported in the LUNG SAFE study[1] included non-cardiogenic shock (7.5 %), and trauma (4.2 %). These should therefore be prioritized for screening so that the cause of AHRF can be rapidly identified in the majority of cases. In rare cases, however, the cause of AHRF remains elusive after an initial diagnostic work-up.[7,8] This occurs more commonly in immunosuppressed patients, where the precise cause of AHRF cannot be identified in up to 15 % of cases.[9] The management of patients in whom the cause of AHRF cannot be identified is a challenge for the intensivist, who must attempt both diagnosis and specific treatment without a clear diagnosis. Although the prognoses of patients with unidentified causes of AHRF remain a subject of debate,[10–12] it is imperative that a comprehensive diagnostic work-up is performed to ensure that curable conditions are not overlooked. This review summarizes the essential elements of the initial diagnostic work-up, then details the main conditions that should be investigated in the setting of AHRF when no ARDS risk factor has been identified. The review does not consider

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https://doi.org/10.1016/j.jointm.2024.09.003
Received 23 July 2024; Received in revised form 11 September 2024; Accepted 23 September 2024
Available online xxx
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Please cite this article as: P. Bay and N. de Prost, Diagnostic approach in acute hypoxemic respiratory failure, Journal of Intensive Medicine, https://doi.org/10.1016/j.jointm.2024.09.003

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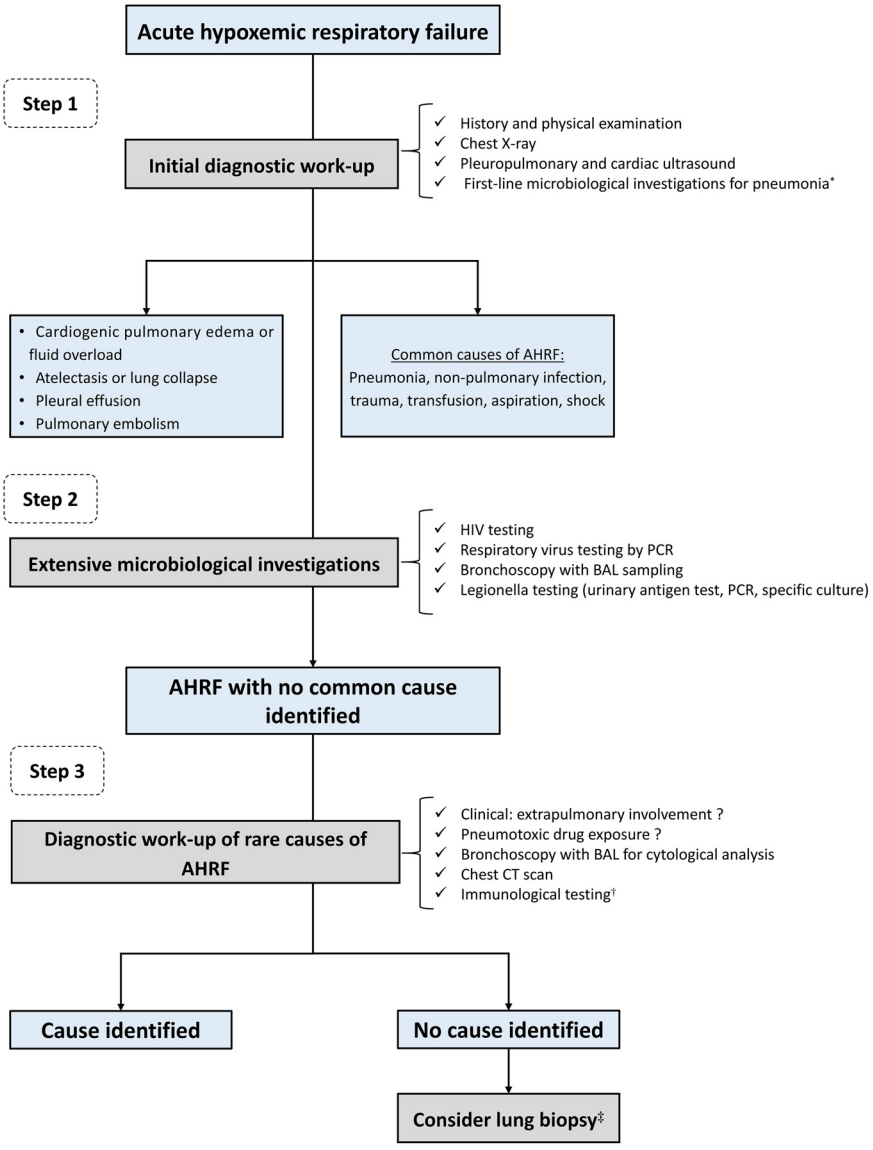
Acute hypoxemic respiratory failure
Step 1
Initial diagnostic work-up
✓ History and physical examination
✓ Chest X-ray
✓ Pleuropulmonary and cardiac ultrasound
✓ First-line microbiological investigations for pneumonia*
• Cardiogenic pulmonary edema or fluid overload
• Atelectasis or lung collapse
• Pleural effusion
• Pulmonary embolism
Common causes of AHRF:
Pneumonia, non-pulmonary infection, trauma, transfusion, aspiration, shock
Step 2
Extensive microbiological investigations
✓ HIV testing
✓ Respiratory virus testing by PCR
✓ Bronchoscopy with BAL sampling
✓ Legionella testing (urinary antigen test, PCR, specific culture)
AHRF with no common cause identified
Step 3
Diagnostic work-up of rare causes of AHRF
✓ Clinical: extrapulmonary involvement ?
✓ Pneumotoxic drug exposure ?
✓ Bronchoscopy with BAL for cytological analysis
✓ Chest CT scan
✓ Immunological testing†
Cause identified
No cause identified
Consider lung biopsy‡

Figure 1. Diagnostic approach for application in patients with AHRF. *First-line microbiological investigations for pneumonia include respiratory sample and blood culture, pneumococcal and legionella urinary antigen analysis, and respiratory virus testing via PCR. †Immunological testing includes AAN, anti-ENA panel, rheumatoid factor, anti-CCP antibodies, ANCA, myositis-specific antibodies, and depending on the clinical context, anti-GBM, and anti-GM-CSF antibodies. ‡If the patient is invasively ventilated.
AAN: Antinuclear antibodies; AHRF: Acute hypoxemic respiratory failure; ANCA: Anti-neutrophil cytoplasmic antibody; BAL: Bronchoalveolar lavage; CCP: Cyclic citrullinated peptide; CT: Computed tomography; ENA: Extractable nuclear antigen; GBM: Glomerular basement membrane; GM-CSF: Granulocyte-macrophage colony-stimulating factor; HIV: Human immunodeficiency virus; PCR: Polymerase chain reaction.

airway, vascular, neuromuscular, or chest wall diseases that lead to AHRF.

Initial Diagnostic Work-Up

A pragmatic diagnostic approach in cases of AHRF is summarized in Figure 1. The first step is to rule out cardiogenic pulmonary edema or fluid overload, atelectasis or lung collapse, pleural effusion, and pulmonary embolism – which are at the forefront of acute respiratory distress. In most cases, a thorough medical history focusing on cardiovascular and thromboembolic comorbidities, a complete physical examination, chest X-ray, and cardiac and pleuropulmonary ultrasound[13,14] are sufficient to diagnose these conditions. After these conditions have been investigated and ruled out, the second step is to look for the most common causes of AHRF, such as pneumonia, non-pulmonary infection, trauma, transfusion, aspiration, and shock.[6] These causes can be rapidly identified via history taking and physical examination, medical record review, and laboratory tests. In a large multicenter study conducted in France, no common risk factor could be identified in 7.5 % of ARDS patients.[11] Strikingly, this figure was confirmed in an ancillary analysis of the LUNG SAFE study, in which approximately 8 % of ARDS patients had no ARDS risk factor identified at the time of ARDS recognition.[12] The etiologies of this subgroup can be considered rare causes of AHRF. These patients without identified common causes of AHRF require a very specific etiological diagnostic approach, which we describe in detail below.

Rare Causes of AHRF

It is impossible to provide an exhaustive list of non-infectious rare causes of AHRF, but pragmatically they can be divided into four categories; immune, drug-induced, malignant, and idiopathic. A pragmatic list of the main entities, based on expert opinion,[8,11,12] is provided in Table 1. Identifying situations that suggest a rare cause of AHRF is crucial, even if a common cause appears to have been identified after the initial diagnostic work-up. This is especially true because two causes may be

Table 1
Main non-infectious causes of AHRF with no common risk factors for ARDS identified.

Rare causes of ARDS	Main entities	Associated radiological patterns	BAL findings	Key element of the diagnostic work-up	Highlighted references
Immune	CTDs: Idiopathic inflammatory myositis (ASS, dermatomyositis with anti-MDA-5 antibodies), SLE, rheumatoid arthritis, systemic sclerosis, and mixed CTD	Alveolar consolidations, ground glass opacities with/without signs of lung fibrosis*	Non-specific	Immunological testing: AAN, anti-ENA panel, rheumatoid factor, anti-CCP antibodies, ANCA, myositis-specific antibodies with/without anti-GBM, and anti-GM-CSF antibodies	[34]
	Small-vessel vasculitides: microscopic polyangiitis, granulomatosis with polyangiitis, anti-GBM antibody disease	Ground glass opacities sparing the lung periphery, alveolar consolidation Nodules/excavations	DAH† Lymphocytic alveolitis DAH†		[48]
Drug induced	Amiodarone methotrexate (Methotrexate), bleomycin (Bleomycin) Targeted therapy, immune-checkpoint inhibitors	Ground glass or alveolar opacities with/without signs of lung fibrosis*	Lymphocytes >15 % Eosinophils >15 % Neutrophilic alveolitis	Medical history https://www.pneumotox.com/drug/index/	Pneumotox® [64,66]
Malignant	Lymphangitic carcinomatosis Lepidic adenocarcinoma	Mediastinal lymphadenopathies and/or lung nodules or masses	Lymphocytes >15 % Tumoral cells	Histopathology	[10]
	Hematological malignancies (AML)	Alveolar diffuses opacities	Rare presence of blasts	Bone marrow exam	[73]
Idiopathic	Acute exacerbations of idiopathic pulmonary fibrosis or other underlying ILD	Alveolar consolidations, ground glass opacities and signs of lung fibrosis*	Neutrophils alveolitis (>30 %)	Medical history, CT-scan pattern	[75]
	Acute hypereosinophilic pneumonia	Alveolar opacities and pleural effusion	Eosinophils >25 %	Eosinophilia (blood sample, BAL fluid)	
	Cryptogenic OP	Inverted halo sign, patchy, migrating infiltrates and alveolar consolidations Centrilobular nodules, mosaic air-trapping, and upper lobe distribution Bilateral patchy ground-glass opacities with/without bilateral consolidations, patchy ground-glass opacities	Mixed alveolitis with >15 % lymphocytes Lymphocytes >15 % Neutrophilic alveolitis (>30 %)	CT-scan pattern, BAL fluid findings	
	Acute hypersensitivity pneumonitis				
	Acute interstitial pneumonia				

AAN: Antinuclear antibodies; AHRF: Acute hypoxemic respiratory failure; AML: Acute myeloid leukemia; ANCA: Antineutrophil cytoplasmic antibodies; ARDS: Acute respiratory distress syndrome; ASS: Antisynthetase syndrome;; BAL: Bronchoalveolar lavage; CCP: Cyclic citrullinated peptide; CT: Computed tomography; CTD: Connective tissue disease; DAD: Diffuse alveolar damage; DAH: Diffuse alveolar hemorrhage; ENA: Extractable nuclear antigen; GBM: Glomerular basement membrane; GM-CSF: Granulocyte-macrophage colony-stimulating factor; ILD: Interstitial lung disease.; MDA-5: Anti-melanoma differentiation-associated protein 5; NSIP: Non-specific interstitial pneumonia; OP: Organizing pneumonia; SLE: Systemic lupus erythematosus; UIP: Usual interstitial pneumonia.

* Signs of lung fibrosis: reticulations, traction bronchiectasis, honeycombing.

† Bloody BAL fluid (i.e., alveolar red blood cells) and/or hemosiderin-laden macrophages on Perls staining with a Golde score >100 or >60 % alveolar siderophages.

associated, for example, an infection may occur in addition to a flare-up of an immune disorder.[15]

Several clinical features may cause clinicians to suspect rare causes of AHRF, including a previous history of immune disease or exposure to a known pneumotoxic drug, a subacute presentation (i.e., onset of respiratory symptoms >7 days but <30 days prior to presentation), the presence of extrapulmonary manifestations, or an unresolved pneumonia with adequate antibiotic treatment and no microbiological documentation.[8,16] Importantly, the onset of respiratory symptoms in <7 days, although less suggestive, should not lead clinicians to rule out an unusual cause. Bronchoalveolar lavage (BAL) fluid analysis and chest computed tomography (CT), although often non-specific, can prompt suspicion of a rare cause of AHRF. Certain CT patterns are suggestive of a rare cause of AHRF, including diffuse or patchy ground-glass lung infiltrates, signs of underlying interstitial lung disease (ILD) (e.g., subpleural reticulations, traction bronchiectasis), or pulmonary nodules with or without cavitation. In the absence of clinical, radiological, or BAL cytology evidence suggesting a rare cause of AHRF, comprehensive microbiological investigations are necessary, particularly if symptoms started <7 days before and the patient became febrile.

Comprehensive microbiological investigations

Microbiological documentation is lacking in 40 %–60 % of cases of severe community-acquired pneumonia, and should therefore not be the only criterion for ruling out the diagnosis.[17–19] Rapid improvement of AHRF with antibiotic therapy strongly supports an infectious etiology, and may justify delaying further microbiological investigations. However, if there is no improvement despite appropriate antibiotic therapy, further investigation is warranted. The presence of immunosuppression is a key factor guiding additional microbiological testing. Currently, it seems appropriate to perform the following tests in all patients regardless of their immunosuppression status: *Legionella* testing, human immunodeficiency virus testing, respiratory virus testing by polymerase chain reaction (PCR), and bronchoscopy with BAL sampling. New molecular tools such as the BioFire® FilmArray® Pneumonia Panel (Biomérieux, Marcy l'Etoile, France) may be useful,[20,21] particularly when antibiotic therapy has been used prior to conventional microbiological culture. Aggressive testing for *Legionella* is essential, using a combination of assessments including repeated urinary antigen tests at intervals ≥24 h, and specific respiratory sample culture. *Legionella* PCR (specific or multiplex PCR), although not recommended,[22] can reportedly yield better diagnostic results than urinary antigen testing,[23] though it should be combined with other tests. Pathogens known to be difficult to culture, such as atypical bacteria (e.g., *Mycoplasma pneumoniae, Chlamydia pneumoniae, Chlamydia psittaci, Coxiella burnetii, Leptospira* spp.) should also be investigated via PCR or specific serological tests, depending on the time elapsed since the onset of symptoms. Non-respiratory viruses (e.g., Hantavirus, viral hem-

orrhagic fevers) can also cause pneumonia, but these are often associated with multisystemic manifestations.[24] In such cases, PCR or serology may also be helpful. In immunosuppressed patients, the search for pathogens should be more comprehensive, and tailored to the type of immunosuppression.[25] Fungal (e.g., pneumocystosis, aspergillosis, emerging invasive fungal infections) and viral (e.g., cytomegalovirus, herpes simplex virus) evaluations need to be comprehensive, incorporate the analysis of chest CT patterns, and potentially include bronchoscopy, BAL analysis, tests for specific biomarkers, and PCR tests. Lastly, metagenomics, an emerging unbiased pan-pathogen molecular approach, may also be of use in these challenging diagnostic situations.[26–28]

Immune causes

Pulmonary involvement in immune diseases may present as AHRF requiring ICU admission. Typically, there are associated suggestive extrapulmonary manifestations (e.g., skin, kidney, joint, muscle), but some patients may present with isolated pulmonary involvement.

Connective tissue diseases (CTDs)

CTDs are the most common autoimmune disorders seen in the ICU, particularly in cases of AHRF.[8,29–31] The term rapidly progressive interstitial lung disease (RP-ILD), the definition of which is not universally agreed upon, is often used to describe AHRF associated with CTD.[32] In such patients, the pulmonary manifestations of idiopathic inflammatory myopathies (IIMs), a group of rare CTDs characterized by varying degrees of muscle inflammation,[33] are emblematic due to their frequency during disease progression and the severity of respiratory impairment.[34] The two most commonly implicated subtypes of IIMs are antisynthetase syndrome and dermatomyositis with anti-melanoma differentiation-associated protein 5 (MDA-5) antibodies. Antisynthetase syndrome has been characterized as the association of inflammatory myositis, ILD, arthritis, Raynaud's phenomenon, and mechanic's hands with the presence of anti-aminoacyl-tRNA-synthetase (ARS) antibodies.[35] Other symptoms overlapping with Sjögren's syndrome and systemic sclerosis are also quite commonly reported. A total of eight ARS antibodies have been identified. Although anti-JO1 antibodies are the most common, forms with anti-PL7, anti-PL12, and anti-EJ antibodies appear to be associated with greater respiratory severity.[35–38] In addition to ARS antibodies, anti-MDA-5 antibodies were discovered in 2005 in patients with clinically amyopathic dermatomyositis (CADM), thus they were initially termed anti-CADM antibodies.[39] Dermatomyositis with anti-MDA-5 antibodies is most commonly characterized by respiratory involvement, skin involvement, Raynaud's syndrome, and joint involvement.[40,41] Muscle involvement is variable and often mild when present, justifying the term amyopathic dermatomyositis. Lung involvement is sometimes isolated, making diagnosis more difficult. The reputation of the disease is based on the frequency and severity of lung involvement.[34,42,43] Vuillard et al.,[34] analyzed a multicenter cohort of patients with anti-synthetase or anti-MDA-5 antibodies presenting with AHRF requiring ICU admission, and reported that the latter had dramatically higher in-hospital mortality than the former (29 % *vs.* 84 %) despite aggressive management. In cases requiring extracorporeal membrane oxygenation, mortality can reach 100 % without emergency lung transplantation.[42] Pulmonary involvement in other IIMs is rarer, more chronic, and less aggressive, and therefore much less common in ICU patients.[33] Other CTDs that occasionally present with ILD leading to AHRF include rheumatoid arthritis, scleroderma, primary Sjögren's syndrome, and mixed CTD.[31,44] Systemic lupus erythematosus – with or without antiphospholipid syndrome – can cause severe and abrupt AHRF associated with diffuse alveolar hemorrhage (DAH) related to pulmonary capillaritis, which is accompanied by acute glomerulonephritis in more than two-thirds of cases and can be the inaugural manifestation of the disease.[31,45] Similarly, antiphospholipid syndrome may present as AHRF, particularly as DAH in cases of catastrophic syndrome[46] Other CTDs, including rheumatoid arthritis, systemic sclerosis, and mixed CTD, can also present as AHRF, but this is much rarer and often occurs in the setting of underlying ILD. In this situation, a thorough assessment is essential to rule out alternative diagnoses, particularly infections, before concluding a disease flare-up.

Vasculitides

AHRF requiring ICU admission may complicate or, in up to 90 % of cases, reveal small-vessel vasculitides,[47,48] mostly granulomatosis with polyangiitis and microscopic polyangiitis. Patients may present with isolated acute respiratory failure (approximately one-third of cases), typically related to DAH, or with a pulmonary-renal syndrome (approximately one-third of cases), defined as the association of DAH with rapidly progressive glomerulonephritis. Eosinophilic granulomatosis with polyangiitis can present as a severe exacerbation of asthma, sometimes associated with pulmonary infiltrates.[49] Early identification of patients with vasculitis flares is necessary to initiate targeted treatment and prevent worsening of acute respiratory failure and renal function deterioration, which can lead to renal death. Anti-neutrophil cytoplasmic antibody (ANCA) testing, using high-quality proteinase 3 and myeloperoxidase ANCA immunoassays as opposed to indirect immunofluorescence, is now recommended as the preferred initial screening method and has high diagnostic accuracy in selected patients.[49,50]

Anti-glomerular basement membrane (GBM) disease is a rare cause of DAH, and typically presents as a pulmonary-renal syndrome. Circulating anti-GBM antibodies can be detected with high specificity by enzyme-linked immunosorbent assays in >90 % of patients. Notably, however, clinicians should be aware that negative test results may be due to all the antibodies being fixed to their target (lung and kidney), or to a lack of sensitivity. In the latter clinical setting, renal biopsy can be performed, and typically indicates extracapillary glomerulonephritis with linear immunoglobulin G deposits along the GBM. In patients with anti-GBM disease, urgent immunosuppression and plasma exchange are required to prevent permanent loss of renal function.[51] It remains uncertain whether patients with ANCA-associated vasculitis benefit from plasma exchange.[52,53]

Other immune diseases

Less commonly, autoinflammatory diseases can present as AHRF. Although predominantly seen in pediatrics, it is important to be aware of situations that can occur in adults in the ICU. Severe forms of Still's disease may require admission to intensive care, and pulmonary involvement is reported in 75 %

of patients, typically with fever, often associated with cardiac involvement and hemophagocytosis.[54] A transient skin rash, arthralgias, odynophagia, and markedly elevated ferritin levels contribute to the formulation of the diagnosis.[55] COPA syndrome, a recently described monogenic interferon-related autoinflammatory syndrome, is mainly associated with DAH, ILD, and arthritis. Forms with isolated pulmonary involvement have been described, and adult-onset has been documented in a few patients.[56] Positive interferon assessment is a disease marker. Myelodysplastic/myeloproliferative neoplasms are increasingly recognized for their immunological manifestations, and can be associated with pulmonary involvement[57] Prominent examples include non-Langerhans histiocytosis[58,59] and the recently described vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome,[60,61] which can present with AHRF requiring ICU admission. Diagnosis is based on a complete blood count, assessment for extrapulmonary manifestations, and bone marrow biopsy with next-generation sequencing myeloid panel analyses.

Lastly, pulmonary alveolar proteinosis (PAP) is a disease characterized by abnormal accumulation of surfactant in the alveoli, and alveolar macrophage dysfunction. PAP results in progressive dyspnea of insidious onset. Primary PAP is characterized by the disruption of granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling. Autoimmune PAP is caused by elevated levels of GM-CSF autoantibodies, and accounts for >90 % of all cases.[62,63]

Drug-induced causes

Extensive lists of drugs have been reported as causes of drug-induced pneumonias that can lead to AHRF. To our knowledge, no studies have reported the prevalence of drug-related causes in patients admitted to the ICU with AHRF, but several studies have addressed this issue in patients with ARDS. Dhokarh et al.[64] reported that in a retrospective cohort of 514 ARDS patients, 9.5 % could be classified as having drug-induced ARDS. In a study conducted by Gibelin et al.,[11] 26 % of patients with ARDS and no common risk factor identified – 7.5 % of the whole cohort – were ultimately diagnosed with drug-induced ARDS, with chemotherapeutic agents and amiodarone being the most common culprits. Anan et al.[65] reported that in a retrospective cohort of 197 patients with ARDS, 13.7 % could be classified as being drug-induced. In fact, all drugs can be associated with pulmonary adverse effects, with a wide spectrum of clinical and radiological patterns (e.g., chronic ILD, ARDS, DAH, eosinophilic pneumonia), making diagnosis particularly challenging for clinicians. The drug-induced respiratory disease website (pneumotox.com) can be a useful tool in this regard. Patients at higher risk of pulmonary toxicity include those of older age, those with pre-existing lung diseases including ILD and lung cancer, and lung surgery patients.[66] The main drugs involved are amiodarone, bleomycin (Bleomycin), methotrexate (Methotrexate), mechanistic target of rapamycin inhibitors, cyclophosphamide and other alkylating agents, and anti-CD20 therapies.[66] Thoracic radiotherapy is also a classic cause of acute lung injury that can lead to AHRF, particularly in the presence of underlying ILD.[67]

Immune-checkpoint inhibitors, which represent the latest breakthrough in oncology, have recently been reported to cause immune-related adverse events.[68] These include several pulmonary complications such as sarcoid-like granulomatosis, pleural effusion, exacerbation of obstructive lung disease, and most notably, checkpoint inhibitor pneumonitis (CIP).[68] Of these complications, CIP is the most widely recognized, and is of serious concern due to its high morbidity and mortality rates. The incidence of CIP in clinical trials has been reported to be <6 %. This claim has been challenged by real-world data, however, which have indicated higher rates ranging from 10 % to 20 %. Several factors have been shown to increase the risk of CIP, including the use of programmed cell death protein (PD-1) or programmed cell death protein ligand agents (vs. cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4] inhibitors), combination immunotherapy (CTLA-4 and PD-1 combination *vs.* monotherapy), radiotherapy, and the organ of tumor origin (e.g., non-small cell lung cancer *vs.* renal cell or other cancer types).[68,69] The clinical presentation of CIP includes dyspnea, cough, and hypoxemia, either at rest or on exertion. These symptoms may appear soon after treatment initiation, typically within days to weeks. The reported timeframes vary between study cohorts, but the reported median onset is approximately 2–3 months after starting on immune-checkpoint inhibitors. The most common radiographic patterns found are ground-glass opacities, organizing pneumonitis, and hypersensitivity pneumonitis.[69]

Malignant causes

Several cancers can be revealed as a result of AHRF, and fulfill the clinical and radiological criteria for ARDS,[11] including mainly solid cancers with lymphangitic carcinomatosis and lung adenocarcinomas. Mediastinal/hilar lymphadenopathies and/or pulmonary nodules or masses on chest CT may help to raise clinical suspicion, and guide the diagnostic strategy. Lepidic adenocarcinoma is a well-differentiated adenocarcinoma that develops along intact alveolar septa without stromal, pleural, or vascular invasion,[70] and its clinical and radiological presentation may mimic pneumonia.[71] Cytological analysis of respiratory samples (sputum or BAL) enables diagnosis. Small cell neuroendocrine carcinoma is a rare but well-known cause of AHRF in the ICU.[72] Among the hematological malignancies, acute myeloid leukemia is most commonly associated with pulmonary involvement, which may be secondary to pulmonary leukostasis, pulmonary leukemic infiltration, and acute lysis pneumopathy.[25,73] In-hospital mortality is particularly high in these patients, approaching 50 % according to a multicenter, international, prospective study.[74]

Idiopathic diseases

Acute interstitial pneumonia refers to an idiopathic form of AHRF characterized histologically by the presence of diffuse alveolar damage in the absence of exposure to ARDS risk factors, and no other identified cause, including CTD and drug exposure.[75,76] It affects patients of all ages and both sexes, and is often preceded by a flu-like illness. The duration of symptoms in the original series ranged from 2 days to 11 days.[76] Physical findings are non-specific and do not include the digital clubbing seen in patients with acute exacerbations of idiopathic pulmonary fibrosis/usual interstitial pneumonia, which are chronic

forms of idiopathic lung disease. Treatment is based on supportive care and high-dose intravenous steroids, although the level of evidence is low.[76] Mortality has ranged from 50 % to 100 % in previously reported series.[76] Cryptogenic organizing pneumonia is a subacute idiopathic interstitial pneumonia[77] characterized by patchy and often migratory multifocal alveolar consolidations and a rapid response to steroids, but frequent relapses. Acute eosinophilic pneumonia can have an abrupt and severe onset, presenting with ARDS criteria, and may be idiopathic, although identifiable causes such as smoking and inhalation exposures, medications, and infections have been reported.[78] Marked BAL fluid eosinophilia (>25 %) is a key feature of its diagnosis. Peripheral blood eosinophilia may be absent in the early stages of the disease, and a marked increase occurs after corticosteroids are initiated, peaking 4–5 days thereafter.[79] A rapid clinical response is typically achieved within 24–48 h of corticosteroid initiation.

Pragmatic diagnostic approach for rare causes of AHRF

When faced with a patient with AHRF without an apparent cause after an initial diagnostic work-up, it is appropriate to perform a comprehensive microbiological evaluation (Fiure 1), guided by possible underlying immunosuppression, bronchoscopic BAL analysis, and high-resolution chest CT. BAL is a high-risk procedure in non-intubated patients, with the potential for secondary deterioration. A non-invasive strategy has been shown to have comparable diagnostic performance to an invasive approach in onco-hematological patients with AHRF.[80] In non-intubated patients, BAL should only be considered after a well-executed non-invasive strategy. If the diagnostic work-up remains negative at this stage, a comprehensive search for the main causes of ARDS with no risk factor is required, using a multidisciplinary approach. First, a detailed history and physical examination are essential to look for possible extra-respiratory symptoms, signs, and exposure to pneumotoxic drugs. Second, a comprehensive immunological assessment is required, including antinuclear antibodies, anti-extractable nuclear antigen panel, rheumatoid factor, anti-cyclic citrullinated peptide (CCP) antibodies, ANCA, myositis-specific antibodies and – depending on the clinical context – anti-GBM and anti-GM-CSF antibodies. The presence of a macroscopically bloody BAL in the absence of bronchial hemorrhage is associated with DAH in >80 % of cases,[81,82] and together with the presence of extrapulmonary symptoms (e.g., arthralgias, renal involvement), it is highly suggestive of an immune cause.[83] If a diagnosis remains elusive a lung biopsy approach may be considered,[7,14] but this strategy is only feasible in invasively ventilated patients. Previous observational series have reported high diagnostic performance of open lung biopsy in selected patients.[10,84–86] Specifically, in a meta-analysis conducted by Libby et al.,[85] open lung biopsy was associated with a high diagnostic performance of 84 % in ARDS patients, with resulting changes in patient management in 73 % of cases. Other studies have reported lower diagnostic performance, however,[87] and the potential complications of the procedure are substantial, with reported complication rates of 25 %–35 %.[84,86] These reported complications are mainly related to air leaks, which can sometimes be fatal. The specificity of histological findings is also questionable. Therefore, the decision to perform a diagnostic open lung biopsy should only be considered in a multidisciplinary context, after the failure of a comprehensive and well-conducted non-invasive approach in the face of ARDS with no identified risk factors and unfavorable evolution, most often after a trial of high-dose corticosteroids.[14] Notably, of the 2813 ARDS patients managed in the LUNG SAFE study, only 11 (0.4 %) underwent open lung biopsy, indicating that the vast majority of ARDS cases are managed without a lung biopsy.[1] The roles of less invasive techniques such as cryobiopsies and transbronchial biopsies remain to be determined in the ICU setting.

Conclusions

Rapid identification of the cause of AHRF is essential in order to facilitate the initiation of targeted treatment as soon as possible. Patients with AHRF in whom no common cause has been identified should rapidly undergo a comprehensive and hierarchical diagnostic work-up aimed at categorizing the underlying disease as immune, drug-induced, malignant, or idiopathic. A multidisciplinary approach involving intensivists and organ specialists is required to determine which patients may benefit from a particular intervention such as immunosuppression, removal of pneumotoxic drugs, or corticosteroid therapy.

CRediT authorship contribution statement

Pierre Bay: Writing – review & editing, Writing – original draft, Conceptualization. **Nicolas de Prost:** Writing – review & editing, Validation, Supervision, Conceptualization.

Acknowledgments

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics statement

Not applicable.

Conflict of interest

N.D.P. has served as an advisor or speaker for Moderna and AstraZeneca.

Data availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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